

Claims

1. Use of a compound of general formula I, formulae I to VIII , formulae 2 to 12, and the compounds of tables 1 and 8 for the preparation of a medicament.
2. Use of a compound of general formula 1, formulae I to VIII , formulae 2 to 12, and the compounds of tables 1 and 8 for the preparation of a medicament for the treatment of arrhythmia.
3. Use according to the preceding claim where said arrhythmia is a reentry arrhythmia of either atrial or ventricular origin, including repolarisation alternans arrhythmia where both supraventricular and ventricular tachyarrhythmias may present as tachycardia, flutter or fibrillation.
4. Use of a compound of general formula 1, formulae I to VIII , formulae 2 to 12, and the compounds of tables 1 and 8 for the preparation of a medicament for prevention and/or treatment of slowed conduction in the heart.
5. Use of a compound of general formula 1, formulae I to VIII , formulae 2 to 12, and the compounds of tables 1 and 8 for the preparation of a medicament for improvement of contractility of the heart.
6. Use of a compound of general formula 1, formulae I to VIII , formulae 2 to 12, and the compounds of tables 1 and 8 for the preparation of a medicament for treatment of disease states associated with impaired GJIC during metabolic stress, including glucose and oxygen deprivation.
7. Use of a compound of general formula 1, formulae I to VIII , formulae 2 to 12, and the compounds of tables 1 and 8 for the preparation of a medicament for antithrombotic treatment.
8. Use of a compound of general formula 1, formulae I to VIII , formulae 2 to 12, and the compounds of tables 1 and 8 for the preparation of a medicament useful in prevention and /or treatment of osteoporosis.

9. Use of a compound of general formula 1, formulae I to VIII , formulae 2 to 12, and the compounds of tables 1 and 8 for the preparation of a medicament useful in prevention and /or treatment of joint diseases including arthritis.
10. Use of a compound of general formula 1, formulae I to VIII , formulae 2 to 12, and the compounds of tables 1 and 8 for the preparation of a medicament useful in prevention and /or treatment of disease in poorly vascularized cartilage and joints including arthritis.
11. Use of a compound of general formula 1, formulae I to VIII , formulae 2 to 12, and the compounds of tables 1 and 8 for the preparation of a medicament useful in prevention and /or treatment of bone loss and increasing the healing of bone fractures.
12. Use of a compound of general formula 1, formulae I to VIII , formulae 2 to 12, and the compounds of tables 1 and 8 for the preparation of a medicament useful in prevention and /or treatment of vascularization of the cornea in disease states with poor nutrition of the cornea and to increase the healing of corneal lesions.
13. Use of a compound of general formula 1, formulae I to VIII , formulae 2 to 12, and the compounds of tables 1 and 8 herein for the preparation of a medicament useful in treatment of wounds and in particular ischemic ulcers.
14. Use of a compound of general formula 1, formulae I to VIII , formulae 2 to 12, and the compounds of tables 1 and 8 herein for the preparation of a medicament useful in the treatment of gastric and duodenal ulcers.
15. Use of a compound of general formula 1, formulae I to VIII , formulae 2 to 12, and the compounds of tables 1 and 8 that increase gap junctional coupling and/or GJIC in the vascular wall for the preparation of a medicament for the prevention and/or treatment of hypertension.
16. Use of a compound of general formula 1, formulae I to VIII , formulae 2 to 12, and the compounds of tables 1 and 8 herein for the preparation of medicaments useful in preventing ischemic damage in the brain and for the treatment of organic psychoses that may present with symptoms, such as depression, anxiety, learning and memory deficit, phobias, or hallucinations.

17. Use of a compound of general formula 1, formulae I to VIII , formulae 2 to 12, and the compounds of tables 1 and 8 herein for the preparation of a medicament useful in prevention and /or treatment of cataract.
18. Use of a compound of general formula 1, formulae I to VIII , formulae 2 to 12, and the compounds of tables 1 and 8 herein for the preparation of a medicament useful in prevention and /or treatment of deafness associated with impaired GJIC.
19. Use of a compound of general formula 1, formulae I to VIII , formulae 2 to 12, and the compounds of tables 1 and 8 for the preparation of a medicament useful in prevention and /or treatment of gastrointestinal motility disorders.
20. Use of a compound of general formula 1, formulae I to VIII , formulae 2 to 12, and the compounds of tables 1 and 8 for the preparation of a medicament useful in the treatment of female infertility that is due to poor cell-to-cell coupling in the ovaries.
21. Use of a compound of general formula 1, formulae I to VIII , formulae 2 to 12, and the compounds of tables 1 and 8 for the preparation of a medicament useful along with oxytocin for the induction and facilitation of labour.
22. Use of a compound of general formula 1, formulae I to VIII , formulae 2 to 12, and the compounds of tables 1 and 8 herein for the preparation of a medicament useful in treatment of male infertility associated with impaired cell-to-cell coupling.
23. Use of a compound of general formula 1, formulae I to VIII , formulae 2 to 12, and the compounds of tables 1 and 8 herein for the preparation of a medicament useful in improving glucose tolerance in a subject with non-insulin dependent diabetes mellitus due to impaired GJIC between β -cells.
24. A method of treatment of arrhythmia comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of general formula 1, formulae I to VIII , formulae 2 to 12, and the compounds of tables 1 and 8.
25. A method of treatment according to the preceding claim wherein said arrhythmia is a reentry arrhythmia of either atrial or ventricular origin, including repolarisation alternans arrhythmia where both supraventricular and ventricular tachyarrhythmias may present as tachycardia, flutter or fibrillation comprising administering to a patient in need of such

treatment a therapeutically effective amount of a compound of general formula 1, formulae I to VIII, formulae 2 to 12, and the compounds of tables 1 and 8.

26. A method of increasing the gap junctional intercellular communication of mammalian cells subjected to glucose and/or oxygen deprivation comprising administering an effective amount of a compound of general formula 1, formulae I to VIII , formulae 2 to 12, and the compounds of tables 1 and 8.

27. A method of antithrombotic treatment comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of general formula 1, formulae I to VIII , formulae 2 to 12, and the compounds of tables 1 and 8.

28. A method of treatment of osteoporosis comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of general formula 1, formulae I to VIII , formulae 2 to 12, and the compounds of tables 1 and 8.

29. A method of treating or preventing bone loss and increasing the healing of bone fractures comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of general formula 1, formulae I to VIII , formulae 2 to 12, and the compounds of tables 1 and 8.

30. A method of treatment of joint diseases including arthritis comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of general formula 1, formulae I to VIII , formulae 2 to 12, and the compounds of tables 1 and 8.

31. A method of treatment of cancer in tissue of endodermal, mesodermal or ectodermal origin, including carcinomas and hepatocellular and cholangiocellular neoplasms and bone cancer comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of general formula 1, formulae I to VIII, formulae 2 to 12, and the compounds of tables 1 and 8.

32. A method of treatment of wounds and in particular ischemic ulcers comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of general formula 1, formulae I to VIII , formulae 2 to 12, and the compounds of tables 1 and 8.

33. A method of treatment of wounds or lesions in skin comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of general formula 1, formulae I to VIII , formulae 2 to 12, and the compounds of tables 1 and 8.

34. A method of treatment of wounds or lesions in oral mucosa comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of general formula 1, formulae I to VIII , formulae 2 to 12, and the compounds of tables 1 and 8.

35. A method of treatment of gastric and duodenal ulcers comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of general formula 1, formulae I to VIII , formulae 2 to 12, and the compounds of tables 1 and 8.

36. A method of treating or preventing hypertension by increasing gap junctional coupling and/or GJIC in the vascular wall comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of general formula 1, formulae I to VIII , formulae 2 to 12, and the compounds of tables 1 and 8.

37. A method of preventing ischemic damage in the brain and treating organic psychoses that may present with symptoms such as depression, anxiety, learning and memory deficit, phobias, or hallucinations comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of general formula 1, formulae I to VIII , formulae 2 to 12, and the compounds of tables 1 and 8.

38. A method of treatment of deafness associated with impaired GJIC comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of general formula 1, formulae I to VIII , formulae 2 to 12, and the compounds of tables 1 and 8.

39. A method of treatment of gastrointestinal motility disorders comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of general formula 1, formulae I to VIII , formulae 2 to 12, and the compounds of tables 1 and 8.

40. A method of treatment of female infertility that is due to poor cell-to-cell coupling in the ovaries comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of general formula 1, formulae I to VIII , formulae 2 to 12, and the compounds of tables 1 and 8.
41. A method of induction of and facilitation of labour comprising administering along with oxytocin to a patient in need of such treatment a therapeutically effective amount of a compound of general formula 1, formulae I to VIII , formulae 2 to 12, and the compounds of tables 1 and 8.
42. A method of treatment of male infertility associated with impaired cell-to-cell coupling comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of general formula 1, formulae I to VIII , formulae 2 to 12, and the compounds of tables 1 and 8.
43. A method of improving glucose tolerance in a subject with non-insulin dependent diabetes mellitus due to impaired GJIC between β -cells comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of general formula 1, formulae I to VIII , formulae 2 to 12, and the compounds of tables 1 and 8.
44. A method of treating or preventing disease in poorly vascularized cartilage and joints comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of general formula 1, formulae I to VIII , formulae 2 to 12, and the compounds of tables 1 and 8.
45. A method according to the preceding claim wherein said disease is arthritis.
46. A method of treating or preventing cataract comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of general formula 1, formulae I to VIII , formulae 2 to 12, and the compounds of tables 1 and 8.
47. A method of treating or preventing vascularization of the cornea in disease states with poor nutrition of the cornea and increasing the healing of corneal lesions comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of general formula 1, formulae I to VIII , formulae 2 to 12, and the compounds of tables 1 and 8.

48. A method of treating or preventing growth and spreading of cancer cells comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of general formula 1, formulae I to VIII , formulae 2 to 12, and the compounds of tables 1 and 8.

49. A method for the treatment of pancreatitis in a patient suffering therefrom comprising administering to said patient an effective amount of a compound of general formula 1, formulae I to VIII, formulae 2 to 12, and the compounds of tables 1 and 8.

50. A method of treatment of glucose and oxygen deprivation of cells, a tissue, or an organ in a patient suffering therefrom comprising administering to said patient an effective amount of a compound of general formula 1, formulae I to VIII , formulae 2 to 12, and the compounds of tables 1 and 8.

51. A method according to the preceding claim wherein said organ is the heart.

52. A method of preventing or treating a non-proliferative disease comprising administering a therapeutically effective amount of a compound that facilitates intercellular communication as determined by effect in the CaCl_2 arrhythmia mouse model.

53. A method according to claim 52 wherein said compound has a score in said mouse model of 2 or 3.

54. The method of claim 52 wherein said compound facilitates gap junctional intercellular communication.

55. The method of claims 52-54 wherein said compound is an agonist of an antiarrhythmic peptide receptor.

56. The method of claims 52-55, wherein said compound is selected from the group consisting of resveratrol including including the various isomers, dimers, trimers, tetramers and derivatives thereof.

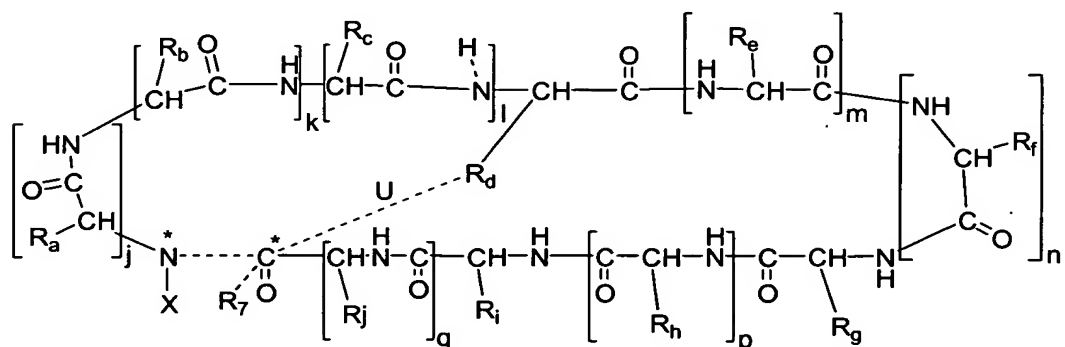
57. The method of claim 56, wherein the compound is trans-resveratrol (trans-3,5,4'-trihydroxystilbene).

58. The method of claims 52-54, wherein said compound is a selected from the group consisting of irsogladine or (6-(2,5-dichlorophenyl)-2,4-diamino-1,3,5-triazine) and derivatives thereof.

59. The method of claims 52-54, wherein said compound is selected from the group consisting of the aporphinoid alkaloids, preferably boldine and taspine and derivatives thereof.

60. A method of preventing or treating a disease characterized by decreased GJIC in the diseased tissue comprising administering a therapeutically effective amount of a compound that facilitates intracellular communication as determined by effect in the calcium chloride arrhythmia mouse model, wherein said compound is selected from the group of compounds having the formula I:

(I)



representing a peptide sequence wherein the amino acid residues may be D- and/or L-forms, and having the N-terminal at N^* and the C-terminal at C^* and being optionally cyclic via a covalent bond between N^* and C^* as shown by a broken line or between R_d and C^* as shown by the broken line U ; the broken line between N^* and C^* , which when present excludes the bond U , represents an optional covalent bond and when said bond is not present then N^* is bound to a hydrogen atom; when the optional covalent bond U between R_d and C^* is present then R_7 is void and the presence of R_7 excludes the bond U ;

and wherein

X represents an N-terminal moiety such as a photoprobe capable of being bonded to the amino terminal N^* , or an acyl group derived from a C(2-22)alkyl carboxylic acid, such as acetic acid, propionic acid, butyric acid and other fatty acids, such as behenic acid,

optionally substituted with one or more substituents selected from the group consisting of hydroxy, halogen, C(1-6)alkyl, nitro and cyano; or X represents hydrogen;

R₇ represents OH, NH₂, NHNH₂, NHR₈ or OR₈ when the bond between N* and C* is missing, or R₇ is absent when there is a bond between N* and C*;

R₈ represents H or a straight or branched C(1-6)alkyl group, an aryl or an aralkyl group.

R_a represents the amino acid side chain of Hyp or Pro;

R_b represents the amino acid side chain of Hyp or Pro;

R_c represents the amino acid side chain of Gly, Sar, an aromatic amino acid side chain optionally substituted with one or more hydroxy, halogen, nitro, cyano, azido, amino, benzoyl or lower alkoxy or thioalkoxy group in the aromatic ring;

R_d represents the amino acid side chain of Ala, Gly, Glu, Asp, Dab, Dapa, Lys, Asn, Gln, Orn, Thr, Ser or Cys;

R_e represents the amino acid side chain of Ala;

R_f represents the amino acid side chain of Ala, Sar or Gly;

R_g represents any amino acid side chain except the side chain of L-4Hyp or a moiety of formula Z or Za;

R_h represents the amino acid side chain of Ala, or R_g represents a moiety of formula Z or Za;

R_i represents the amino acid side chain of Gly or R_i represents an aromatic amino acid optionally substituted with one or more hydroxy, halogen, nitro, cyano, azido, amino, benzoyl or lower alkoxy or thioalkoxy group in the aromatic ring;

R_j represents the amino acid side chain of Asn, Gln, Asp, Glu, Cys or Tyr;

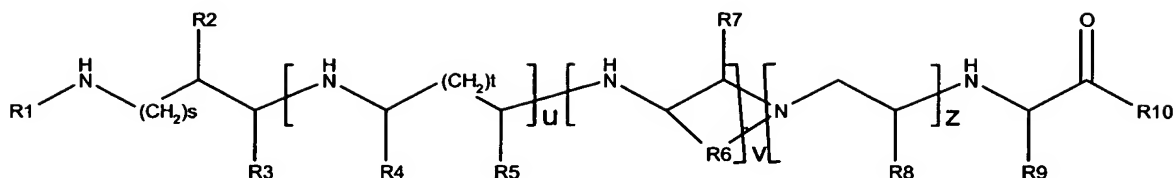
and each of j, k, l, m, n, p and q is independently 0 or 1;

and the retro form, all D form, or retro all-D form of the peptide sequence of formula I, and

salts and amides thereof.

61. The method of claim 60, wherein the disease is any one of the diseases or conditions disclosed herein, preferably inflammation of airway epithelium, disorders of alveolar tissue, wounds, erectile dysfunction, urinary bladder incontinence, impaired hearing due to diseases of the cochlea, endothelial lesions, diabetic retinopathy and diabetic neuropathy, neuropathic pain, ischemia of the central nervous system, spinal cord injuries, dental tissue disorders including periodontal disease, kidney diseases, subchronic and chronic inflammation, cancer and failures of bone marrow or stem cell transplantation.

62. The method of claims 52-61, wherein the compound is represented by any one of the following formulae: (VII)



wherein,

R1 represents H or acetyl (Ac)

R2 represents a sidechain of one of the amino acids G, Y, D-Y, F and D-F,

R3 represents O or H

R4 represents any amino acid sidechain

R5 represents O or H

R6 represents a C(1-4)alkyl group, such as CH₂, (CH₂)₂, (CH₂)₃, and (CH₂)₄

R7 represents O or H

R8 represents O or H

R9 represents a sidechain of one of the amino acids G, Y, D-Y, F and D-F,

R10 represents OH or NH₂,

and S, T, U, V and Z are integers defined as follows

S: 0, 1 or 2

T: 0, 1 or 2

U: 0 or 1

V: 0 or 1

Z: 0 or 1, or

R1-X1-X2-X3-R2 (VIII)

wherein,

X1 is 0, Ala, Gly, β-Ala, Tyr, D-Tyr, Asp, HAA

X2 is 0; Ala-Gly-T4c-Pro; Ala-Sar-Hyp-Pro; Ala-6ring-; Ala-Asn; D-Asn-D-Ala; D-Asn; γAbu; Gly, Ala; D-Ala; β-Ala; Pamh; Asn; or HAA;

X3 is Tyr; D-Tyr; Gly, Pamb, or Phe; and

R1 is H or Ac, with the proviso that X1 and X2 are not both 0;

and salts thereof.

63. The method of claims 52-61, wherein the half life of the compound as measured in a standard stability assay is more than 50 minutes and preferably more than 5 hours.
64. The method of claims 52-61, wherein the half life of the compound as measured in a standard stability assay is more than 5 hours.
65. A method of treating inflammation of airway epithelium comprising administering to a patient in need of such treatment a therapeutically effective amount of at least one compound of the compounds disclosed herein that facilitates intercellular communication.
66. A method of treating injuries that trigger brain inflammatory responses, including head injury and ischemia, neurodegenerative diseases including Parkinson's disease, autoimmune diseases, infectious diseases, prion diseases, and brain tumors comprising administering to a patient in need of such treatment a therapeutically effective amount of at least one compound disclosed herein that facilitates intercellular communication.
67. A method of treating reactive gliosis caused by stroke comprising administering to a patient in need of such treatment a therapeutically effective amount of at least one compound disclosed herein that facilitates intercellular communication.
68. A method of treating or preventing the development of glial neoplasms comprising administering to a patient in need of such treatment a therapeutically effective amount of at least one compound disclosed herein that facilitates intercellular communication.
69. A method of treating neuronal and muscular symptoms related to spinal cord axotomy comprising administering to a patient in need of such treatment a therapeutically effective amount of at least one compound disclosed herein that facilitates intercellular communication.
70. A method of preventing or treating diabetic retinopathy comprising administering to a patient in need of such treatment a therapeutically effective amount of at least one compound disclosed that facilitates intercellular communication.
71. A method of treating vascular abnormalities in the retina as for instance arteriosclerosis comprising administering to a patient in need of such treatment a

therapeutically effective amount of at least one compound disclosed herein that facilitates intercellular communication.

72. A method of treating ischemia comprising administering to a patient in need of such treatment an amount of at least one compound disclosed herein that facilitates intercellular communication which is effective in providing capillary sprouting.

73. A method of improving the vascular healing process after balloon catheter injury in the carotid comprising administering to a patient in need of such treatment a therapeutically effective amount of at least one compound disclosed herein that facilitates intercellular communication.

74. A method of treating erectile dysfunction comprising administering to a patient in need of such treatment a therapeutically effective amount of at least one compound disclosed herein that facilitates intercellular communication.

75. A method of treating urge incontinence comprising administering to a patient in need of such treatment a therapeutically effective amount of at least one compound disclosed herein that facilitates intercellular communication.

76. A method of treating a wound comprising administering to a patient in need of such treatment a therapeutically effective amount of at least one compound disclosed herein that facilitates intercellular communication.

77. A method of treating subchronic or chronic inflammation by providing a local increase in synthesis of immunoglobulins comprising administering to a patient in need of such treatment a therapeutically effective amount of at least one compound disclosed herein that facilitates intercellular communication.

78. A method of treating peripheral neuropathy and neuropathic pain comprising administering to a patient in need of such treatment a therapeutically effective amount of at least one compound disclosed herein that facilitates intercellular communication.

79. A method of preventing or treating acquired or age dependent hearing loss comprising administering to a patient in need of such treatment a therapeutically effective amount of at least one compound disclosed herein that facilitates intercellular communication.

80. A method of treating reduced capacity of haematopoietic tissue, such as in haematological malignancies and after treatment with chemotherapeutics, comprising administering to a patient in need of such treatment a therapeutically effective amount of at least one compound disclosed herein that facilitates intercellular communication.

81. A method of preventing or treating a disease characterized by dysregulation of renal gap junction communication caused by heavy metal poisoning, non-infectious inflammation or microbial infection comprising administering to a patient in need of such treatment a therapeutically effective amount of at least one compound disclosed herein that facilitates intercellular communication.

82. A method of treating inappropriate hormone secretion from the anterior pituitary gland comprising administering to a patient in need of such treatment a therapeutically effective amount of at least one compound disclosed herein that facilitates intercellular communication.

83. A method of prevention or treatment of disturbed development of teeth comprising administering to a patient in need of such treatment a therapeutically effective amount of at least one compound disclosed herein that facilitates intercellular communication.

84. A method for the amelioration of skin aging, cellulite and wrinkles comprising administering to a patient in need of such treatment a therapeutically effective amount of at least one compound disclosed herein that facilitates intercellular communication.

85. A method of treatment of tobacco related disease associated with uncoupling of gap junctions, such as impaired wound healing and aging of skin, in a patient suffering therefrom comprising administering to said patient an effective amount of at least one compound disclosed herein that facilitates intercellular communication.

86. The methods of claims 52-85, wherein the compound administered is the compound disclosed in any one of claims 52-62.

87. The method of claims 52-86, wherein the administered compound is at least one of

HPP-5-K6-OH

H-AAP-10-K6-OH

Cyclo(retro-AAP-10-Asn)
 Ac-Retro(AAP-10)-(all D)-NH₂
 Ac-Retro(AAP-10)-OH

HPP-5-K6-NH₂

H-[D-Hyp⁴]AAP-10-NH₂
 H-[D-Pro⁴, Ala⁵]AAP-10-NH₂
 AAP-10-K6-NH₂
 H-C(Acm)GAGHypPYC(Acm)-NH₂
 H-AAP-10-Asn-NH₂
 Cyclo(AAP-10-Asn)
 Cyclo(AAP-10-Gln)
 H-HypPYNGAG-NH₂
 H-GAG-T4c-PY-NH₂
 H-GA-Sar-Hyp-PY-NH₂
 H-Sar-A-Sar-Hyp-PY-NH₂
 H-GAG-Pc-PY-NH₂
 H-GAGGPY-NH₂
 H-GAG-DHypAY-NH₂
 H-GAG-DHyp-DProY-NH₂
 des-Hyp⁴-[Asn⁵]AAP-10-NH₂
 AcGNY
 GNY
 H-GANY-NH₂
 H-DY-DN-G-NH₂
 H-YNG-NH₂
 H-GGY-NH₂
 H-G-DN-Y-NH₂
 H-Y-DN-G-OH
 Ac-Y-DN-G-OH
 Ac-G-D-N-Y-NH₂
 Ac-Y-D-N-G-NH₂ and
 H-GK(DNP)Y-NH₂

and salts thereof.

88. The method of claims 52-86, wherein said compound is selected from the group consisting of resveratrol and its isomers and polymers.

89. The method of claims 52-86, wherein said compound is selected from the group consisting of aporphinoid alkaloids, preferably boldine and taspine and their derivatives.

90. A pharmaceutical composition comprising a compound of general formula 1, formulae I to VIII , formulae 2 to 12, and the compounds of tables 1 and 8 or according to any one of the preceding claims, and a pharmaceutically acceptable carrier or diluent.
91. A composition according to the preceding claim which is an enteric tablet.
92. A composition according to claim 89 which is an injection preparation.